

ORIGINAL ARTICLE

Angioedema without urticaria in childhood

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Abstract**Background:** There has been no separate study investigating angioedema without urticaria (Aw/oU) exclusively in children so far. The purpose of this study was to investigate the frequency, clinical presentation, etiology, management and follow-up of Aw/oU in children.**Methods:** This is a prospective study that included all consecutive patients with a history of Aw/oU referred to our clinic between January 2011 and May 2012. A standard diagnostic and therapeutic algorithm was applied to all patients.**Results:** The frequency of Aw/oU was found to be 1.6% during the study period. An etiological factor could be found in only 45 patients (49%). The causes of Aw/oU were infection (21%), allergy (14%), thyroid autoimmunity (TA)-related (8%) and nonsteroid anti-inflammatory drug hypersensitivity (6%), and idiopathic angioedema (51%). There was no hereditary type I, II or acquired type of angioedema or rare syndromes associated with Aw/oU. The median follow-up was 16 months (range: 12–30 months). Antihistamine prophylaxis was initiated at therapeutic doses in 20 patients with frequently recurrent angioedema due to idiopathic and euthyroid TA-related Aw/oU for 3 months. These patients responded to antihistamine prophylaxis for 3 months. Four patients relapsed after cessation of prophylaxis at the end of 3 months. Antihistamine prophylaxis was prolonged to 6 months in three patients and to 9 months in one patient.**Conclusions:** Angioedema without urticaria in children is a rare condition and no etiology can be identified in half of them. Antihistamine treatment alone is sufficient, and prognosis is good in recurrent non hereditary cases in a short-term follow-up period.

Angioedema is a reversible, localized swelling of the deep cutaneous layers, caused by mediators that enhance vascular permeability (1). Angioedema commonly occurs together with urticaria, but it may also appear separately (2). The etiology of angioedema without urticaria (Aw/oU) is often different from that of urticaria or urticaria with angioedema (2–4). Angioedema is the main characteristic feature of hereditary angioedema (HAE); therefore, most of the published reports about it belong to this rare disease entity (5). Although angioedema has been reported to become the dominant acute allergic non-asthmatic disease resulting in hospitalization (6), there are only limited reports in adults (7, 8). Most of the data about children with Aw/oU obtained from adult studies including children (9, 10) or from studies on chronic urticaria or HAE (2, 5). There has been no study investigating Aw/oU exclusively in children so far. The purpose of this study was to investigate the frequency, clinical presentation, etiology, management, and follow-up of Aw/oU in children.

Patients and methods

This prospective study was performed in the outpatient clinic of the Pediatric Allergy and Asthma Unit of Gazi University Hospital. All consecutive patients with a history of Aw/oU referred to our clinic between January 2011 and May 2012 were included. Patients with a history of anaphylaxis or urticaria on admission were not included. The study was approved by Gazi University Hospital Ethics Committee, and written informed consent was obtained from all patients and/or their parents.

A detailed history including timing, duration, frequency, localization, potential triggers (insect bites, foods, drugs, aeroallergens as in the case of angioedema seen with allergic conjunctivitis and infections), associated symptoms/signs, response to previous treatments, comorbid diseases, and family history was taken. A complete physical examination was carried out. All cases were managed according to a diagnostic and therapeutic algorithm (Fig. 1).

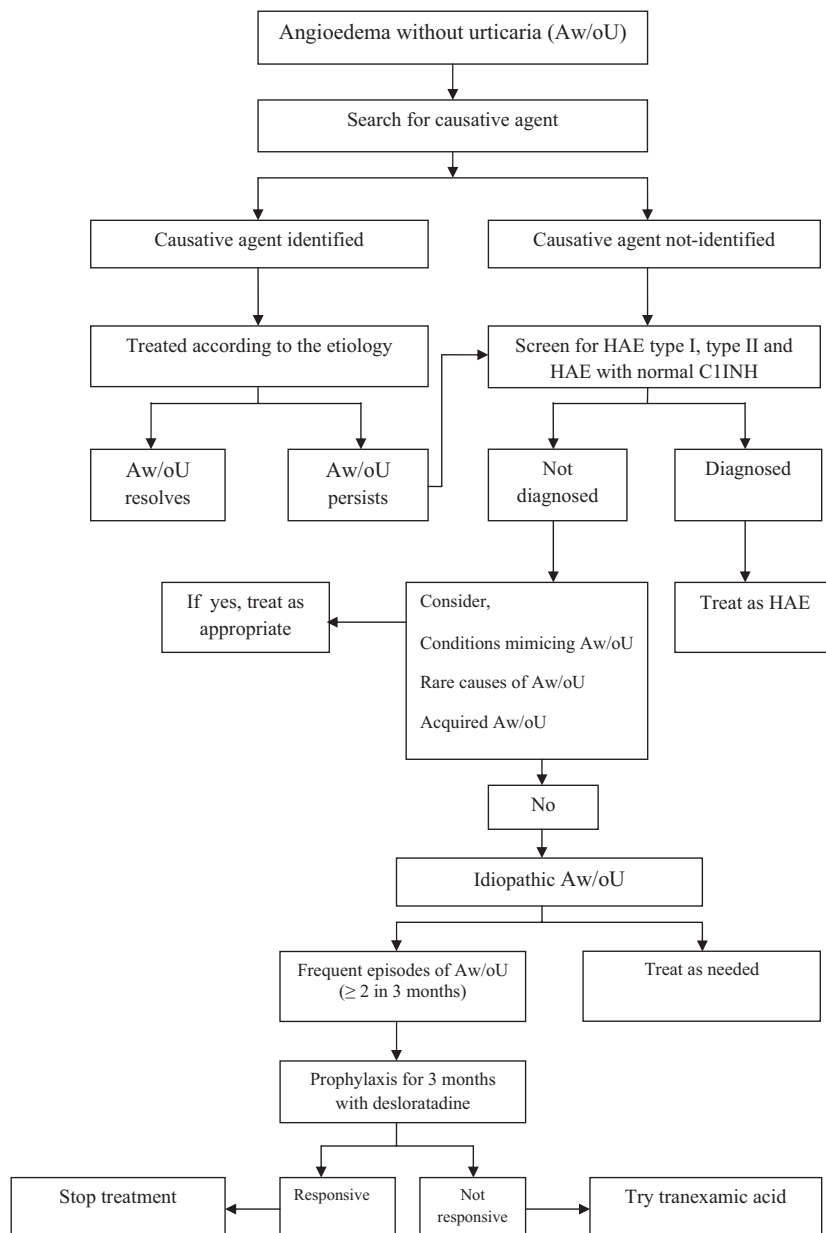


Figure 1 Diagnostic and therapeutic algorithm proposed for children with Aw/oU.

Laboratory investigations

The following laboratory investigations were performed to all patients with Aw/oU: complete blood count, erythrocyte sedimentation rate, complement levels including C3 and C4, urine analysis, antithyroid peroxidase antibody (anti-TPO) and antithyroglobulin antibody (anti-T), skin prick test (SPT) with a panel of aeroallergens. Additional investigations were determined according to medical history and physical examination and primary laboratory tests. They included urine/throat culture, SPT and/or intradermal tests and/or provocation tests with suspected food or drugs, thyroid function tests, and ultrasonography. Serum C1 inhibitor

(C1INH) level and function were studied if no causative agent was identified or serum C4 level was low or a family history of Aw/oU was present or frequent (≥ 2 episodes within 3 months).

Definitions

Angioedema was defined as asymmetric, non-dependent, and non-pitting swelling of the deeper layers of the skin and mucous membranes that resolves without scarring or discoloration (11). Angioedema that is not associated with urticaria is defined as Aw/oU. More than one episode of Aw/oU was defined as multiple episode of Aw/oU. Frequently, recurrent

Aw/oU was defined as ≥ 2 episodes of Aw/oU within the last 3 months on admission.

Hereditary angioedema (HAE) is a rare autosomal dominant disorder defined as recurrent angioedema episodes without urticaria that affect the skin, gastrointestinal tract, or upper airways. Type I, with low C1INH antigenic protein and functional activity; and type II, with normal or elevated protein level but low C1INH function; and the other form of HAE with normal C1INH protein level and function may occur with F12 mutation or with an unknown cause (12, 13).

Acquired C1 inhibitor deficiency is analogous in its presentation to HAE-I/II, except that a family history is lacking and angioedema generally develops after the age of 40 yrs due to a lymphoproliferative or autoimmune disorder (14).

If angioedema was present simultaneously with symptoms/signs of infection such as fever and hypersensitivity to concurrently used drugs was excluded by provocation tests, it is termed as infection-associated Aw/oU.

Angioedema was described as allergic Aw/oU if it was related to food, insect bite, latex, or allergic rhinoconjunctivitis.

Exclusion of other etiological factors together with presence of thyroid autoantibodies was defined as thyroid autoimmunity (TA)-related Aw/oU.

If no underlying etiological factors were detected, angioedema was accepted as idiopathic Aw/oU.

Management

All patients with Aw/oU were followed in three-month intervals. Prophylaxis with an antihistamine (oral desloratadine 2.5 mg for children < 6 yrs of age and 5 mg for children ≥ 6 yrs of age per day) was started for patients with frequently recurrent angioedema due to idiopathic and euthyroid TA-related Aw/oU on admission. If angioedema did not recur within 3 months of treatment, the patient was defined as responsive to treatment and the prophylaxis was quitted. Antihistamine treatment was substituted with tranexamic acid in children who were unresponsive to antihistamine treatment within 3 months (15). Relapse was defined as recurrence of angioedema after cessation of prophylaxis. Antihistamine prophylaxis was prolonged for another 3 months in patients who relapsed. Patients with less frequent angioedema episodes (< 2 episodes/3 months) administered antihistamine when needed.

Statistics

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 15.0 software (SPSS, Inc. Chicago, IL). A descriptive analysis was used for the characterization of patients. Qualitative variables were expressed either in frequencies and percent or median (with minimum and maximum). The univariate analysis to identify variables associated with prophylaxis was investigated using Fisher's exact test. A two-sided value of $p < 0.05$ was considered statistically significant.

Results

Demographics

In the study period of 17 months, of 5918 patients seen in our outpatient clinic, 95 of them (1.6%) presented as Aw/oU. All patients included in the study had documented Aw/oU from medical records, and 27 of the patients (28.4%) had angioedema on referral to our clinic. Demographic and clinical characteristics of the patients are presented in Table 1. The most frequent localization of angioedema was eyelids (Table 1). Fifty-nine patients (62.2%) described angioedema in multiple localizations. Median number of angioedema episodes was 2 (range: 1–25 times). Forty-three patients (45.3%) had personal history of atopic disease. The most frequent comorbidity was allergic rhinitis both in patients and in their family (Table 1). On admission, 52 patients (54.7%) described a suspected agent related to angioedema in history (Table 2). Eighty-three patients (87.4%) described improvement with antihistamines and/or single-dose systemic corticosteroids in history (Table 2). No patients needed either injection of epinephrine or emergency intubation or tracheostomy for angioedema.

Etiology

Etiological investigations could not be performed in three patients because the parents did not give consent. These three patients were responsive to antihistamines in history. Therefore, final etiological analysis was carried out in 92

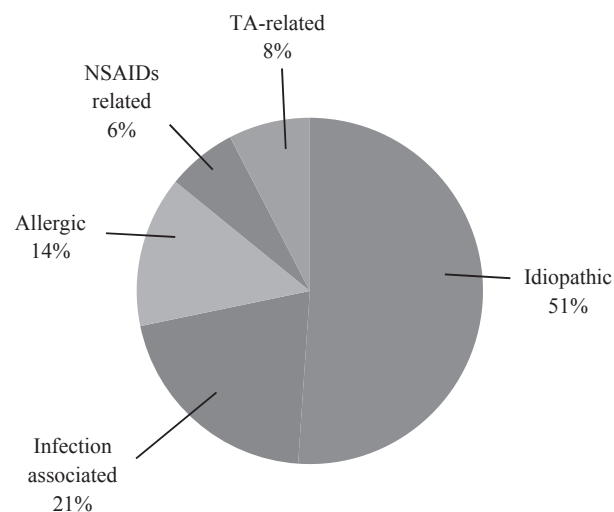
Table 1 Demographic and clinical characteristics of the study group (n = 95)

Male gender, n (%)	68 (71.6)
Age, yrs	8 (0.7–17)
Age of onset of first episode, yrs	7 (0.6–17)
Duration of lesion, h	24 (2–120)
Episode within the last 12 months	2 (0–10)
Frequency of the episode, n (%)	
Single episode	22 (23.2)
Multiple episode	73 (76.8)
Localization of angioedema, n (%)	
Periorbital	71 (74.4)
Lip	53 (55.8)
Extremities	26 (27.4)
Genitalia	8 (8.4)
Ear	7 (7.4)
Tongue	4 (4.2)
Personal history of atopic diseases, n (%)	
Allergic rhinitis	39 (41.1)
Asthma	15 (15.8)
Atopic eczema	10 (10.5)
Family history of atopic diseases, n (%)	
Allergic rhinitis	29 (30.9)
Asthma	15 (16)
Atopic eczema	7 (7.4)
Angioedema without urticaria	17 (17.8)

Continuous variables are shown as median (min–max).

Table 2 Clues in history of children with Aw/oU (n = 95)

	n (%)
Suspicious agent in history	
No suspicious agent	43 (45.3)
Drug	31 (32.6)
Infection	7 (7.4)
Allergic rhinoconjunctivitis	5 (5.3)
Stinging insect bite	4 (4.2)
Food	4 (4.2)
Latex	1 (1.1)
Treatment response in history	
Antihistamine	57 (60)
Antihistamine and single-dose systemic steroid	26 (27.4)
Improves without treatment	12 (12.6)

**Figure 2** Final etiological classification of Aw/oU in children (n = 92).

patients. Final etiological classification of the study group was demonstrated in Fig. 2. No etiological factor could be identified in 47 patients. There were 17 patients with low serum C4 levels; two of them had also low serum C3 levels. Serum C1INH level and its function were studied in 33 patients (35.8%). There was no HAE type I, II, or acquired angioedema or rare syndromes associated with Aw/oU in our study group. Angioedema was related to infections in 19 patients (common cold: 17 patients; streptococcal pharyngitis: 1 patient; urinary tract infection: 1 patient) (Fig. 2). Angioedema was described as allergic in 13 patients (allergic conjunctivitis in 5, stinging insect bite in 5, food allergy in 2, and latex allergy in 1 patient). There were no patients using angiotensin-converting enzyme inhibitors (ACE-I) or estrogen-containing medicine in the study group. Fifty-five oral provocation tests were carried out in 31 patients with suspected drugs. Drugs used in the provocation tests were non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and paracetamol. Six of these patients were diagnosed as having NSAID hypersensitivity. Provocation tests with the other drugs were negative. Twelve patients

(13%) had thyroid autoantibodies (anti-TPO: 11 patients; anti-T: 2 patients). All of these patients were euthyroid.

Management and follow-up

All patients in the study were followed up in three-month intervals notwithstanding the etiological classification. The median follow-up was 16 months (range: 12–30 months). During this period, prophylaxis with desloratadine was initiated to 17 patients with idiopathic Aw/oU (36.1%) and 3 patients with euthyroid TA-related Aw/oU (42.8%) ($p = 1.00$). Sixteen patients took antihistamine prophylaxis for 3 months. Four patients needed a longer period of prophylaxis because of relapse after cessation of the antihistamine (two patients with idiopathic and one patient with euthyroid TA-related Aw/oU for 6 months, one patient with euthyroid TA-related Aw/oU for 9 months). All patients who had TA-related Aw/oU have been followed by pediatric endocrinology department.

Discussion

This study for the first time investigated Aw/oU in children who referred to a tertiary pediatric allergy center. We documented the frequency, etiology, management, and follow-up of this entity. The frequency of Aw/oU in children seems to be very low. An underlying cause was present in half of these cases. Prognosis was good in recurrent non-hereditary Aw/oU in the short-term follow-up.

We found four studies about angioedema including children in published reports (9, 10, 16, 17). The first study is a case series consisted of 10 children in a ten-year period in which half of the children were reported to have rash (16). Two other long-term studies included cases aged between 1–87 years old and 9 months–92 yrs old; however, the percentage of children and the etiological distribution in children were not reported separately (9, 10). The last study consisted of cases with a mean age of 39.4 yrs, which also included children ≥ 15 years old (17). In this study, the authors reported 55 patients with Aw/oU, 28 of whom had systemic symptoms. Therefore, our study is different from previous studies in two points: It includes only children, and it does not include angioedema with urticaria and/or anaphylaxis.

We found the frequency of Aw/oU as 1.6% in children. The lifetime prevalence of non-hereditary angioedema was reported as 4.9 and 7.4% in two nationwide studies (8, 18). Prevalence rates may differ based on the population studied, methods used (questionnaire-based vs physician-based), and the clinics (primary care vs tertiary care) that conduct the study. However, this study is not designed to determine the prevalence of Aw/oU in children rather it is cross-sectional one and included only cases referred to a pediatric allergy clinic. We presume that the frequency rate might be higher if the study had been conducted in pediatric emergency department.

We could identify a triggering factor for Aw/oU in half of the children. In this group, the most frequent precipitating factor seems to be infections followed by allergic diseases, thyroid autoimmunity, and NSAID hypersensitivity.

Infections seem to be the leading trigger of Aw/oU in children in whom a factor could be identified, which is similar to acute urticaria in children (19). Different infectious agents were reported to be associated with Aw/oU in children and adults including Chlamydia, parvovirus, Helicobacter pylori, and parasites (9, 20–22). Two-thirds of our patients had no angioedema at the time of admission to our clinic, which limited investigations about infections. We determined infectious etiology by history in patients who administered to our clinic after resolution of angioedema with compatible symptoms such as fever and rhinorrhea.

Allergic factors as triggers of Aw/oU (14%) were the second most common identified etiologies in children, which was similar to adults (16%) (9). Allergic conjunctivitis and stinging insect bite seem to cause Aw/oU in children more frequently than other allergies. However, when angioedema is associated with urticaria, the probability of allergy as the underlying factor is increasing (3).

The association between TA and chronic urticaria is a known entity in adults (23–25). On the other hand, TA is reported among rare causes of angioedema (1). Zingale et al. (9) reported that 21 patients among 776 with angioedema without urticaria had autoimmune disorders, 8 of whom had autoimmune thyroiditis. We cannot certainly talk about a cause–effect relationship between Aw/oU and TA in our patients because all of them were euthyroid and had no symptoms or signs pointing to a thyroid disease. However, most autoimmune disorders develop by time and Aw/oU in these children may be the preliminary sign of these autoimmune diseases similar to the results of long-term studies with chronic urticaria (26).

Many different drugs were reported to trigger Aw/oU (4). Most widely recognized ones are ACE-I and NSAIDs (6, 7). One-third of our patients gave a history related with drug intake, mostly in the context of infection. However, only 6.5% of our patients were found to have challenge-proven drug hypersensitivity associated with Aw/oU. All of these patients were diagnosed as cross-reactive NSAID hypersensitivity. Angioedema is the most frequent presenting symptom and

sign in children with NSAID hypersensitivity (27). However, clinical history is not a reliable tool for diagnosis and drug provocation tests should be performed before drug elimination (28).

Idiopathic Aw/oU is a diagnosis of exclusion, and it is a poorly understood entity (29). No etiological factor could be identified in half of children with Aw/oU despite extensive investigations, which were compatible with other studies reporting idiopathic angioedema between 33.5% and 46% (7, 9, 10). Three types of idiopathic angioedema were reported: One type is responsive to antihistamines, the other is responsive to tranexamic acid but unresponsive to antihistamines, and the third type is responsive to neither antihistamines nor to tranexamic acid (9, 15, 29). In our study group, no children with idiopathic Aw/oU had a life-threatening episode and only one-third (17/47) required antihistamine prophylaxis. They were all responsive to this treatment (histaminergic idiopathic Aw/oU).

There are also limitations in our study. Cross-sectional design and single-center experience limit generalization of our study results to the population. Also, the number of study group was not enough to detect HAE in the population, which requires screening of at least 10,000–50,000 cases (14). Certainly, we cannot be sure to exclude HAE with normal C1INH because we could not study FXII mutation, and at this time, there are no commonly agreed upon criteria for diagnosing HAE with normal C1INH (12, 30). On the other hand, we do not think that our patients with a family history of Aw/oU had HAE with normal C1INH because all angioedema episodes were either self-limited or were responsive to antihistamines at therapeutic doses (12). Lastly, a longer follow-up period would probably be better to comment on the prognosis.

In conclusion, this study helps in reducing the gap of knowledge about Aw/oU in children. This is a rare condition in children, and no etiology can be identified in half of them. Prophylactic treatment with an antihistamine and relapse after cessation of prophylaxis seem to be rare indicating good prognosis in the short-term follow-up.

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